C3 cont.

(b) the second sample comprises a plurality of different polynucleotide molecules wherein each different polynucleotide molecule comprises a sequence that is different from the nucleotide sequences of any other polynucleotide molecules in said plurality of different polynucleotide molecules,

wherein at least 75% of the polynucleotide molecules in said first sample are polynucleotide molecules comprising said target nucleotide sequence, thereby evaluating said binding property of said polynucleotide probe.

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33. (Twice Amended) The method of claim 27 wherein at least 90% of the polynucleotide molecules in said first sample are said polynucleotide molecules comprising said target nucleotide sequence.

C4

34. (Twice Amended) The method of claim 33 wherein at least 95% of the polynucleotide molecules in said first sample are said polynucleotide molecules comprising said target nucleotide sequence.

35. (Twice Amended) The method of claim 34 wherein at least 99% of the polynucleotide molecules in said first sample are said polynucleotide molecules comprising said target nucleotide sequence.

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42. (Twice Amended) The method of claim 40 wherein:

C5

(a) the target nucleotide sequence is a sequence of a gene or gene transcript of a cell or organism;

(b) the first sample comprises a polynucleotide sample from a wild-type strain of the cell or organism which expresses the gene or gene transcript; and

(c) the second sample comprises a polynucleotide sample from a deletion mutant of the cell or organism which does not express the gene or gene transcript.

C6

48. (Amended) The method of claim 43 wherein the amount of each polynucleotide molecule that does not comprise the target nucleotide sequence in the first sample differs from the amount of the corresponding polynucleotide molecule in the plurality of different

polynucleotide molecules of the second sample by no more than a factor of 100.

C6 Cont.

49. (Amended) The method of claim 43 wherein the amount of each polynucleotide molecule that does not comprise the target nucleotide sequence in the first sample differs from the amount of the corresponding polynucleotide molecule in the plurality of different polynucleotide molecules of the second sample by no more than a factor of 10.

50. (Amended) The method of claim 43 wherein the amount of each polynucleotide molecule that does not comprise the target nucleotide sequence in the first sample differs from the amount of the corresponding polynucleotide molecule in the plurality of different polynucleotide molecules of the second sample by no more than 50%.

51. (Amended) The method of claim 43 wherein the mean abundance of the polynucleotide molecules that do not comprise the target nucleotide sequence in the first sample differs from the mean abundance of the different polynucleotide molecules in the plurality of different polynucleotide molecules of the second sample by no more than a factor of two.

52. (Amended) The method of claim 43 wherein the mean abundance of the polynucleotide molecules that do not comprise the target nucleotide sequence in the first sample differs from the mean abundance of the different polynucleotide molecules in the plurality of different polynucleotide molecules of the second sample by no more than 50%.

53. (Amended) The method of claim 43 wherein the mean abundance of the polynucleotide molecules that do not comprise the target nucleotide sequence in the first sample differs from the mean abundance of the different polynucleotide molecules in the plurality of different polynucleotide molecules of the second sample by no more than 10%.

54. (Amended) The method of claim 43 wherein the mean abundance of the polynucleotide molecules in the first sample differs from the mean abundance of the different polynucleotide molecules in the plurality of different polynucleotide molecules of the second sample by no more than 1%.

C7

57. (Twice Amended) The method of claim 27 wherein said binding property is a specificity of the polynucleotide probe, wherein said specificity is the amount of said polynucleotide molecules comprising said target nucleotide sequence that bind to said polynucleotide probe relative to the amount of polynucleotide molecules not comprising said target nucleotide sequence that bind to the probe under the same binding conditions.

C8

67. (Twice Amended) A method for evaluating a binding property of a plurality of polynucleotide probes to a target nucleotide sequence wherein each polynucleotide probe in the plurality of polynucleotide probes comprises a predetermined nucleotide sequence,

said method comprising comparing the amount of hybridization of polynucleotides in a first sample to each polynucleotide probe in the plurality of polynucleotide probes with the amount of hybridization of polynucleotides in a second sample to each polynucleotide probe in the plurality of polynucleotide probes, wherein:

(a) the first sample comprises a plurality of polynucleotide molecules comprising said target nucleotide sequence; and

(b) the second sample comprises a plurality of different polynucleotide molecules wherein each different polynucleotide molecule comprises a nucleotide sequence that is different from nucleotide sequence of any other polynucleotide molecules in said plurality of different polynucleotide molecules,

wherein at least 75% of the polynucleotide molecules in said first sample are polynucleotide molecules comprising said target nucleotide sequence, thereby evaluating said binding property of each said polynucleotide probe.

C9

71. (Twice Amended) The method of claim 67 wherein said binding property is a specificity of each polynucleotide probe in the plurality of different polynucleotide probes [is determined], wherein said specificity is the amount of said polynucleotide molecules comprising said target nucleotide sequence that bind to said polynucleotide probe relative to the amount of polynucleotide molecules not comprising said target nucleotide sequence that bind to the probe under the same binding conditions.

Add new claims as follows:

90. (New) The method of any one of claims 27-30, 33-40, 42-54, 61-68, 71-75 and 84-85, wherein said polynucleotide molecules comprising said target nucleotide sequence are the same.

C10

REMARKS

The specification has been amended to correct typographical and editorial errors discovered by Attorneys for Applicant during review of the application. No new matter has been added. A marked version of the paragraphs in the specification which have been amended, with the amendments indicated by bracketing for deletions and underlining for additions, is attached hereto as Exhibit A. A clean version of the paragraphs in the specification, as amended, is attached hereto as Exhibit B.

Claims 1, 3-30, 33-40, 42-75 and 81-85 were pending in the application. In the instant amendment, claims 1, 3-26, 55-56, 69-70 and 81-83 have been canceled, claims 27, 33-35, 42, 48-54, 57, 67 and 71 have been amended, and new claim 90 has been added to more clearly claim the present invention. Upon entry of the above-made amendment, claims 27-30, 33-40, 42-54, 57-68, 71-75, 84-85 and 90 will be pending. A marked version of the amended claims showing changes made is attached hereto as Exhibit C. A clean version of the pending claims, as amended, is attached hereto as Exhibit D.

Claims 27 and 67 have been amended to recite that at least 75% of polynucleotide molecules of polynucleotide molecules in said first sample are polynucleotide molecules comprising said target nucleotide sequence. Support for the amendment is found in the specification at page 6, lines 30-36 and page 29, lines 11-16. Claims 33-35 have been amended similarly. Claims 27 and 67 have also been amended to recite "a binding property" rather than "binding properties."

Claim 42 has been amended to depend on claim 40 rather than the canceled claim 41 so that there is proper antecedent basis.

Claim 48 has been amended to clarify that in the claimed method, the amount of each polynucleotide molecule *that does not comprise the target nucleotide sequence* in the first sample differs from the amount of the corresponding polynucleotide molecule in the plurality of different polynucleotide molecules of the second sample by no more than a factor of 100 such that there is proper antecedent basis. Claims 49-54 have been amended similarly.

Claims 57 and 71 have been amended to make the claim language clearer.

New claim 90 has been added. Support for the new claim is found in the specification at page 9, line 17 through page 10, line 15.

No new matter has been added by these amendments. Entry of the foregoing amendments and the following remarks are respectfully requested.

APPLICANT'S INTERVIEW SUMMARY

Applicant thanks Examiner Betty J. Forman for the courtesies extended during the telephonic interview on July 2, 2002 (hereinafter "the Interview") with Assignee's representative R. Douglas Bradley and Applicant's representatives Adriane M. Antler and Weining Wang. During the interview, the claim rejections under 35 U.S.C. § 112, second paragraph, 35 U.S.C. § 102(b), and 35 U.S.C. § 103(a) were discussed. The references cited in the Office Action were also discussed as they pertain to the claim rejections under 35 U.S.C. § 102(b) and § 103(a). With respect to the rejections under 35 U.S.C. § 112, second paragraph, the Examiner indicated that the amendments proposed by Applicant's representatives (which are included in the amendments hereinabove) would overcome the rejections. With respect to the rejections under 35 U.S.C. § 102(b) and § 103(a), Ms. Antler pointed out that the proposed amendments would also obviate these rejections. The Examiner agreed that the amendments would obviate the rejections if filed. However, the Examiner indicated that the proposed amendments would in her opinion introduce new issues such that a new search would be required. Ms. Antler thus proposed to file a Request for Continued Examination (RCE) with the Amendment, which the Examiner indicated would be a desirable course of action.

THE REJECTIONS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH SHOULD BE WITHDRAWN

Claims 1, 3-30, 33-40, 42-75 and 81-85 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In paragraph 4a of the Office Action, claims 1, 3-30, 33-40, 42-75 and 81-85 are rejected as allegedly being indefinite for omitting essential steps. The Examiner contends that the omitted steps are the method steps for comparing the amount of binding to thereby evaluate binding of probe to target, such as steps of labeling, hybridizing, detecting, measuring and

comparing. Applicant has canceled claims 1, 3-26, 55-56, 69-70 and 81-83, thereby obviating the rejection of these claims. Applicant further respectfully submits that the essential step of the methods as claimed in the remaining claims is the step of comparing which is recited in claims 27 and 67. The other steps, e.g., those steps alleged by the Examiner in the Office Action as being omitted, are not essential steps of the claimed methods in that the claimed methods are directed to evaluating a *binding property* of a polynucleotide probe to a target nucleotide sequence by comparing the difference in the amount of hybridization of polynucleotides in a first sample, in which at least 75% of the polynucleotide molecules are polynucleotide molecules comprising the target nucleotide sequence, to the polynucleotide probe with the amount of hybridization of polynucleotides in a second sample, which comprises a plurality of different polynucleotide molecules each comprising a sequence that is different from the nucleotide sequences of any other polynucleotide molecules in the plurality of different polynucleotide molecules, to the polynucleotide probe. The methods of the invention are not limited to any particular way of obtaining the amounts of hybridization. For example, the methods are equally applicable to amounts of hybridization measured in a hybridization experiment which involves the steps of labeling, hybridizing, detecting, measuring as well as to amounts of hybridization saved in a database. Thus, Applicant respectfully submits that the claims do not contain gaps, and that the rejection should be withdrawn.

In paragraph 4b of the Office Action, claims 1, 3-30, 33-40, 42-75 and 81-85 are rejected as allegedly being indefinite for the recitation of "pure." Applicant has canceled claims 1, 3-26, 55-56, 69-70 and 81-83, thereby obviating the rejection of these claims. Applicant has amended claims 27 and 67 to recite that *at least 75% of polynucleotide molecules of polynucleotide molecules in the first sample are polynucleotide molecules comprising said target nucleotide sequence* (emphasis added). Claims 33-35 have been amended similarly. Thus, Applicant respectfully submits that the rejection under 35 U.S.C. § 112, second paragraph, is obviated and should be withdrawn.

In paragraphs 4e, 4w and 4ee of the Office Action, claims 8-9, 55-56 and 69-70, respectively, are rejected as allegedly being indefinite for the recitation "sensitivity of the probe" because alleged essential steps for determining "sensitivity" are omitted, such omission amounting to a gap between the steps. Applicant has canceled claims 8-9, 55-56 and 69-70. The rejection is therefore obviated and should be withdrawn.

In paragraph 4h of the Office Action, claims 10 and 11 are rejected as allegedly being indefinite for the recitation "specificity of the probe" because alleged essential steps for determining "specificity" are omitted, such omission amounting to a gap between the steps. Applicant has canceled claims 10 and 11. The rejection is therefore obviated and should be withdrawn.

In paragraphs 4z and 4hh of the Office Action, claims 57-58 and 71-72, respectively, are rejected as allegedly being indefinite for the recitation "specificity of the probe" because alleged essential steps for determining "specificity" are omitted, such omission amounting to a gap between the steps. Applicant respectfully submits that the essential step of the methods as claimed in these claims is the step of comparing which is recited in the based claims 27 and 67, respectively. The other steps, e.g., those steps alleged by the Examiner in the Office Action as being omitted, are not essential steps of the claimed methods in that the claimed methods are directed to evaluating *a specificity* of a polynucleotide probe to a target nucleotide sequence by comparing the difference in the amount of hybridization of polynucleotides in a first sample to the polynucleotide probe with the amount of hybridization of polynucleotides in a second sample to the polynucleotide probe. The methods of the invention are not limited to any particular way of obtaining the amounts of hybridization. For example, the methods are equally applicable to amounts of hybridization measured in a hybridization experiment which involves the steps of labeling, hybridizing, detecting, measuring as well as to amounts of hybridization saved in a database. Thus, Applicant respectfully submits that the claims do not contain gaps, and that the rejection should be withdrawn.

THE REJECTION UNDER 35 U.S.C. § 102(b) SHOULD BE WITHDRAWN

Claims 1, 3-30, 33-36, 38-40, 43-45, 48-75 and 81-85 are rejected under 35 U.S.C. § 102(b) as being anticipated by Brown et al., U.S. Patent No. 5,807,522 ("Brown"). Applicant respectfully disagrees with the Examiner for the reasons presented below.

A claim is anticipated under 35 U.S.C. § 102 only if each and every element and limitation as set forth in the claim is found, either expressly described or inherently present, in a single prior art reference. *Glaxo, Inc. v. Novopharm Ltd.*, 52. F.3d 1043, 1047 (Fed. Cir. 1995). There must be *no differences* between the claimed invention and the reference disclosure as viewed by a person of ordinary skill in the field of the invention. *Scripps Clinic & Research*

Fdn. v. Genentech, Inc. 927 F. 2d. 1565, 1576 (Fed. Cir. 1991).

At the outset, Applicant respectfully submits that claims 1, 3-26, 55-56, 69-70 and 81-83 have been canceled, thereby obviating the rejection of these claims. Brown teaches a method and apparatus for forming microarrays of biological samples on a support. Brown also teaches hybridization of nucleic acid samples to the microarray. For example, in its example 1, Brown teaches hybridization to its microarray of two pools of nucleic acids, in which one pool contains random amplification products of the 6 large yeast chromosomes and the other pool contains random amplification products of the 10 small yeast chromosomes. The hybridization values of spots or clones on the array identify to which of the two pools the clones belong and correlate the clone to the location on the yeast genome. Brown's hybridization samples are not samples in which *at least 75% of the polynucleotide molecules are polynucleotide molecules comprising the target nucleotide sequence*. Nor does Brown teach a method of evaluating *a binding property* of a polynucleotide probe to a target nucleotide sequence by comparing the difference in the amount of hybridization of polynucleotides in a first sample, in which *at least 75% of the polynucleotide molecules are polynucleotide molecules comprising the target nucleotide sequence*, to the polynucleotide probe with the amount of hybridization of polynucleotides in a second sample, which comprises a plurality of different polynucleotide molecules each comprising a sequence that is different from the nucleotide sequences of any other polynucleotide molecules in the plurality of different polynucleotide molecules, to the polynucleotide probe. Therefore, Applicant respectfully submits that Brown does not anticipate claims 27 and 67, and the claims dependent thereon, and that the rejection under 37 C.F.R. § 102(b) based on Brown should be withdrawn.

THE REJECTIONS UNDER 35 U.S.C. § 103(a) SHOULD BE WITHDRAWN

Claims 37 and 42 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Brown et al., U.S. Patent No. 5,807,522 ("Brown"). Claims 46-47 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Brown in view of Schena et al., 1995, Science 270:467-470 ("Schena"). Applicant respectfully disagrees with the Examiner for the reasons presented below.

A finding of obviousness under 35 U.S.C. § 103(a) requires a determination that the differences between the claimed subject matter and the prior art are such that the subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the invention

was made. *Graham v. Deere*, 383, U.S. 1 (1956). The relevant inquiry is whether the prior art suggests the invention and whether the prior art provides one of ordinary skill in the art with a reasonable expectation of success. Both the suggestion and the reasonable expectation of success must be found in the prior art. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991).

With respect to the rejection of claims 37 and 42, as discussed above, Brown's hybridization samples are not samples in which *at least 75% of the polynucleotide molecules are polynucleotide molecules comprising the target nucleotide sequence*. Nor does Brown teach or suggest a method of evaluating *a binding property* of a polynucleotide probe to a target nucleotide sequence by comparing the difference in the amount of hybridization of polynucleotides in a first sample, in which *at least 75% of the polynucleotide molecules are polynucleotide molecules comprising the target nucleotide sequence*, to the polynucleotide probe with the amount of hybridization of polynucleotides in a second sample, which comprises a plurality of different polynucleotide molecules each comprising a sequence that is different from the nucleotide sequences of any other polynucleotide molecules in the plurality of different polynucleotide molecules, to the polynucleotide probe. Thus, Brown does not render the base claim 27, and any claims dependent thereon, including claims 37 and 42, obvious. Applicant respectfully submits that the rejection of claims 37 and 42 under 35 U.S.C. § 103(a) based on Brown should be withdrawn.

With respect to the rejection of claims 46-47, as discussed above, Brown does not suggest the claimed methods of evaluating *a binding property* of a polynucleotide probe to a target nucleotide sequence by comparing the difference in the amount of hybridization of polynucleotides in a first sample, in which *at least 75% of the polynucleotide molecules are polynucleotide molecules comprising the target nucleotide sequence*, to the polynucleotide probe with the amount of hybridization of polynucleotides in a second sample, which comprises a plurality of different polynucleotide molecules. Schena teaches monitoring gene expression patterns with a cDNA microarray. In Schena, a sample containing fluorescent molecules prepared from total *Arabidopsis* mRNA of the wild-type and a transgenic cell line overexpressing HAT4 are used to hybridize to the microarray. Schena teaches differential expression measurements of the wild-type and the transgenic cell line of *Arabidopsis* genes using microarrays. Schena does not add what is missing in Brown. Thus, Brown in view of Schena does not render the base claim 27, and any claims dependent thereon, including claims

45-46, obvious. Applicant respectfully submits that the rejection of claims 46-47 under 35 U.S.C. § 103(a) based on Brown and Schena should be withdrawn.

CONCLUSION

Applicant respectfully requests entry of the foregoing amendments and remarks into the file of the above-identified application. Applicant believes that each ground for rejection has been successfully overcome or obviated, and that all the pending claims are in condition for allowance. Withdrawal of the Examiner's rejections and allowance of the application are respectfully requested.

Respectfully submitted,

Date: July 15, 2002

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Enclosures